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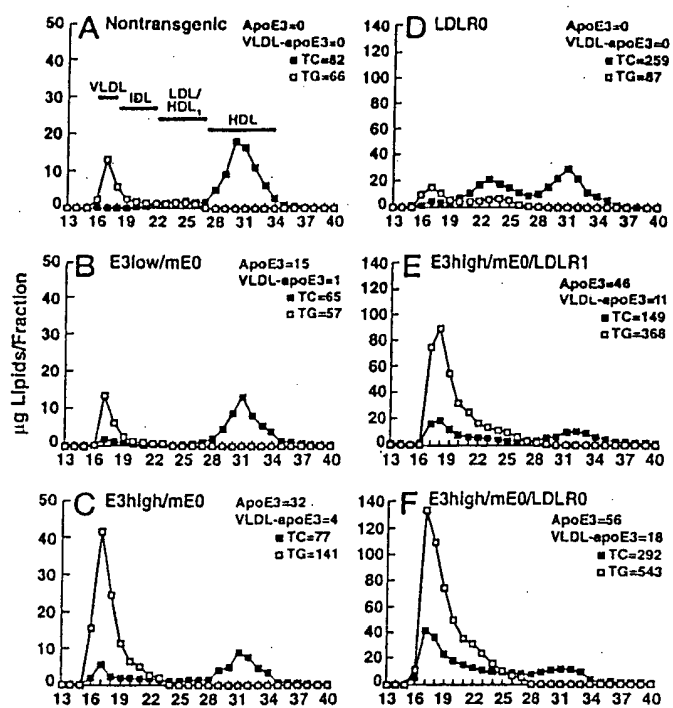


FIG. 1

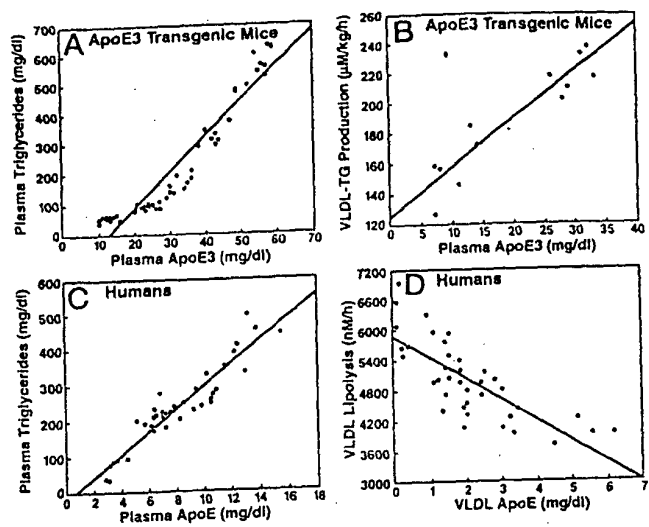


FIG. 2

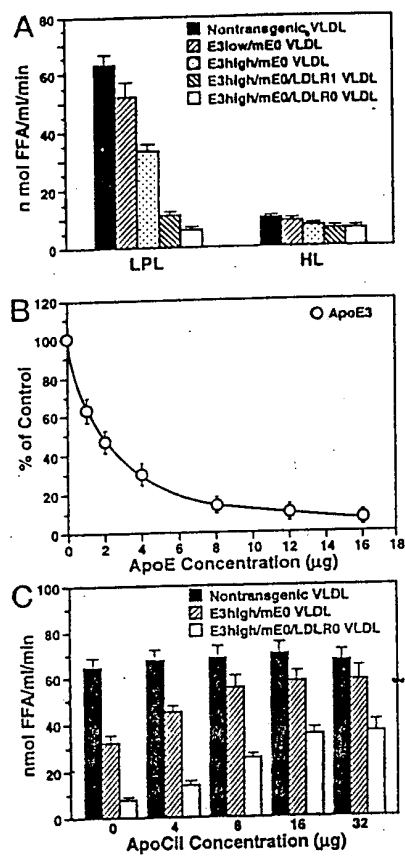


FIG. 3

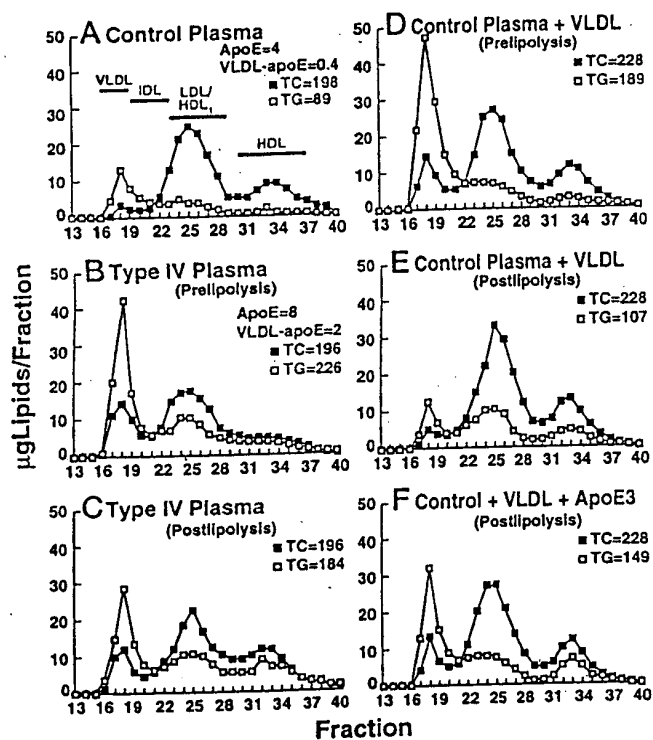


FIG. 4

TABLE I
Lipid and apoE levels in plasma and VLDL from different lines of mice

Mice were in a mixed genetic background (C57BL6/129) and analyzed at 2-4 months of age. TC, total cholesterol; TG, triglycerides; E3, human apoE3; mE, mouse apoE; LDLR, LDL receptor; mE0, homozygous mouse apoE knockout; LDLR1, heterozygous LDL receptor knockout; LDLR0, homozygous LDL receptor knockout.

| Mice | n | Plasma | | | | n | VLDL | | | VLDL-TG production rate |
|------------------|----|-------------|---------------------|-----------------------|-------------------------|---|-------------|---------------------|----------------------|----------------------------|
| | | Human apoE3 | Mouse apoE | TC | TG | | Human apoE3 | Mouse apoE | ApoC-II | |
| | | mg/dl | | | | | μg/mg | | | μm/h/kg |
| Nontransgenic | 18 | 0 | 7 ± 2 | 79 ± 10 | 47 ± 20 | 6 | 0 | 19 ± 4 | 32 ± 6 | 148 ± 18 |
| E3low/mE0 | 12 | 13 ± 2 | 0 | 60 ± 6 ^a | 54 ± 10 | 6 | 23 ± 5 | 0 | 26 ± 5 | 168 ± 19 |
| E3high/mE0 | 15 | 30 ± 4 | 0 | 78 ± 19 | 128 ± 36 ^a | 6 | 38 ± 5 | 0 | 13 ± 2 ^a | 221 ± 11 ^{a,b} |
| LDLR1 | 19 | 0 | 10 ± 3 | 134 ± 14 ^a | 55 ± 18 | 6 | 0 | 24 ± 6 | 25 ± 5 | |
| E3low/mE0/LDLR1 | 13 | 17 ± 2 | 0 | 136 ± 10 ^a | 62 ± 17 | | | | | |
| E3high/mE0/LDLR1 | 17 | 45 ± 4 | 0 | 148 ± 14 ^a | 361 ± 69 ^{a,c} | 6 | 46 ± 4 | 0 | 7 ± 1 ^{a,c} | |
| LDLR0 | 15 | 0 | 15 ± 3 ^a | 255 ± 34 ^a | 86 ± 19 ^a | 6 | 0 | 30 ± 7 ^a | 20 ± 3 ^a | |
| E3low/mE0/LDLR0 | 9 | 23 ± 3 | 0 | 261 ± 11 ^a | 89 ± 18 ^a | | | | | |
| E3high/mE0/LDLR0 | 16 | 54 ± 4 | 0 | 294 ± 37 ^a | 532 ± 59 ^{a,d} | 6 | 55 ± 7 | 0 | 3 ± 1 ^{a,d} | 199 ± 16 ^a |

^a $p < 0.01$ versus nontransgenic mice.

^b $p < 0.05$ versus E3low/mE0 mice.

^c $p < 0.01$ versus LDLR1 mice.

^d $p < 0.01$ versus LDLR0 mice.

FIG. 5

TABLE II
Effect of apoE expression levels of VLDL triglyceride production in
McA-RH7777 cells stably transfected with various apoE isoforms
Values are means of duplicate experiments.

| Cell lines | ApoE in medium | | VLDL triglyceride secretion | |
|-------------|----------------------|------------|-----------------------------|-----------------|
| | Human apoE | Mouse apoE | Without heparinase | With heparinase |
| | ng/mg cell protein/h | | dpm/mg cell protein/4 h | |
| McA-RH7777 | 0 | 353 | 5273 | 5604 |
| McA-Neo | 0 | 368 | 5451 | 5719 |
| McA-apoE2-1 | 309 | 321 | 5193 | 6682 |
| McA-apoE2-2 | 1210 | 332 | 3277 | 8828 |
| McA-apoE2-3 | 2200 | 364 | 2103 | 11576 |
| McA-apoE3-1 | 338 | 327 | 1958 | 6223 |
| McA-apoE3-2 | 1237 | 339 | 1640 | 7815 |
| McA-apoE3-3 | 2436 | 345 | 818 | 9896 |
| McA-apoE4-1 | 318 | 368 | 2878 | 6540 |
| McA-apoE4-2 | 1153 | 347 | 2491 | 8224 |
| McA-apoE4-3 | 2192 | 355 | 832 | 10924 |

FIG. 6

TABLE III
Lipid and apoE levels in plasma and VLDL from normal or type IV hyperlipidemic human subjects
VLDL cholesterol and triglyceride and HDL cholesterol were calculated from the Superpose 6 chromatography profiles of plasma lipoproteins by summing the individual fractions (Fig. 4, A and B). FFA, free fatty acids; TC, total cholesterol; TG, triglycerides.

| Exp. | Plasma | | | | | | | VLDL | | VLDL lipolysis |
|---|--------|-------------------------|-----------------------|---------------------|---------------------|-----------------------|-----------------------|---------------------|---------------------|-------------------------|
| | n | ApoE | TC | VLDL-TC | HDL-TC | TG | VLDL-TG | ApoE | ApoC-II | |
| | | | | mg/dl | | | | μg/mg TG | | nmol FFA/h |
| I. Plasma sample comparisons | | | | | | | | | | |
| Normolipidemic control | 6 | 3.3 ± 0.6 | 193 ± 14 | 6 ± 2 | 54 ± 4 | 69 ± 27 | 22 ± 10 | 13 ± 3 | 39 ± 7 | 6068 ± 579 |
| Type IV-1 200 < TG < 300) | 19 | 8.2 ± 1.9 ^a | 204 ± 27 | 49 ± 7 ^a | 37 ± 7 ^a | 237 ± 24 ^a | 105 ± 13 ^a | 24 ± 3 ^a | 18 ± 3 ^a | 4888 ± 524 ^a |
| Type IV-2 300 < TG < 400) | 4 | 11.1 ± 0.9 ^a | 221 ± 25 | 66 ± 3 ^a | 34 ± 3 ^a | 348 ± 27 ^a | 152 ± 12 ^a | 30 ± 2 ^a | 13 ± 2 ^a | 4252 ± 353 ^a |
| Type IV-3 (TG > 400) | 4 | 13.6 ± 1.3 ^a | 254 ± 15 ^a | 76 ± 9 ^a | 33 ± 6 ^a | 447 ± 36 ^a | 200 ± 23 ^a | 37 ± 2 ^a | 10 ± 2 ^a | 3741 ± 214 ^a |
| II. Effects of apolipoproteins on lipolysis | | | | | | | | | | |
| Control + apoE3 ^b | 6 | 14.0 ± 0 ^a | | | | | | 31 ± 3 ^a | 11 ± 1 ^a | 4132 ± 414 ^a |
| Type IV-2 + apoCII ^c | 4 | | | | | | | | | 5598 ± 198 |

^a $p < 0.01$ versus control.

^b Purified human apoE3 was added to control human plasma at a final concentration of 14 mg/dl. After incubation at 37 °C for 20 min, VLDL were isolated and analyzed for apoE content and LPL-mediated lipolysis.

^c Purified human apoC-II (16 μg) was added to VLDL (30 μg of triglycerides) isolated from plasma of Type IV-2 subjects and its effect on LPL-mediated lipolysis was determined.

FIG. 7

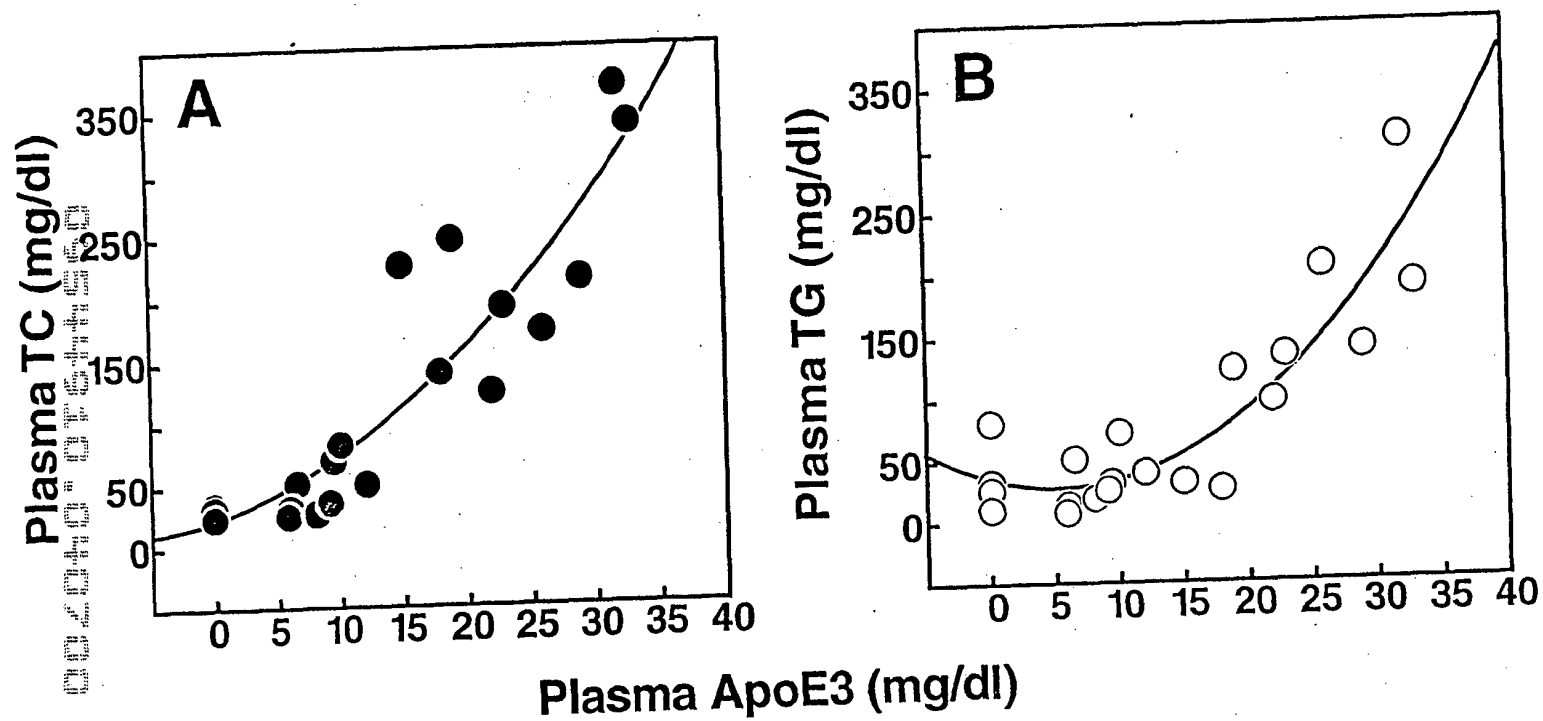


FIG. 8

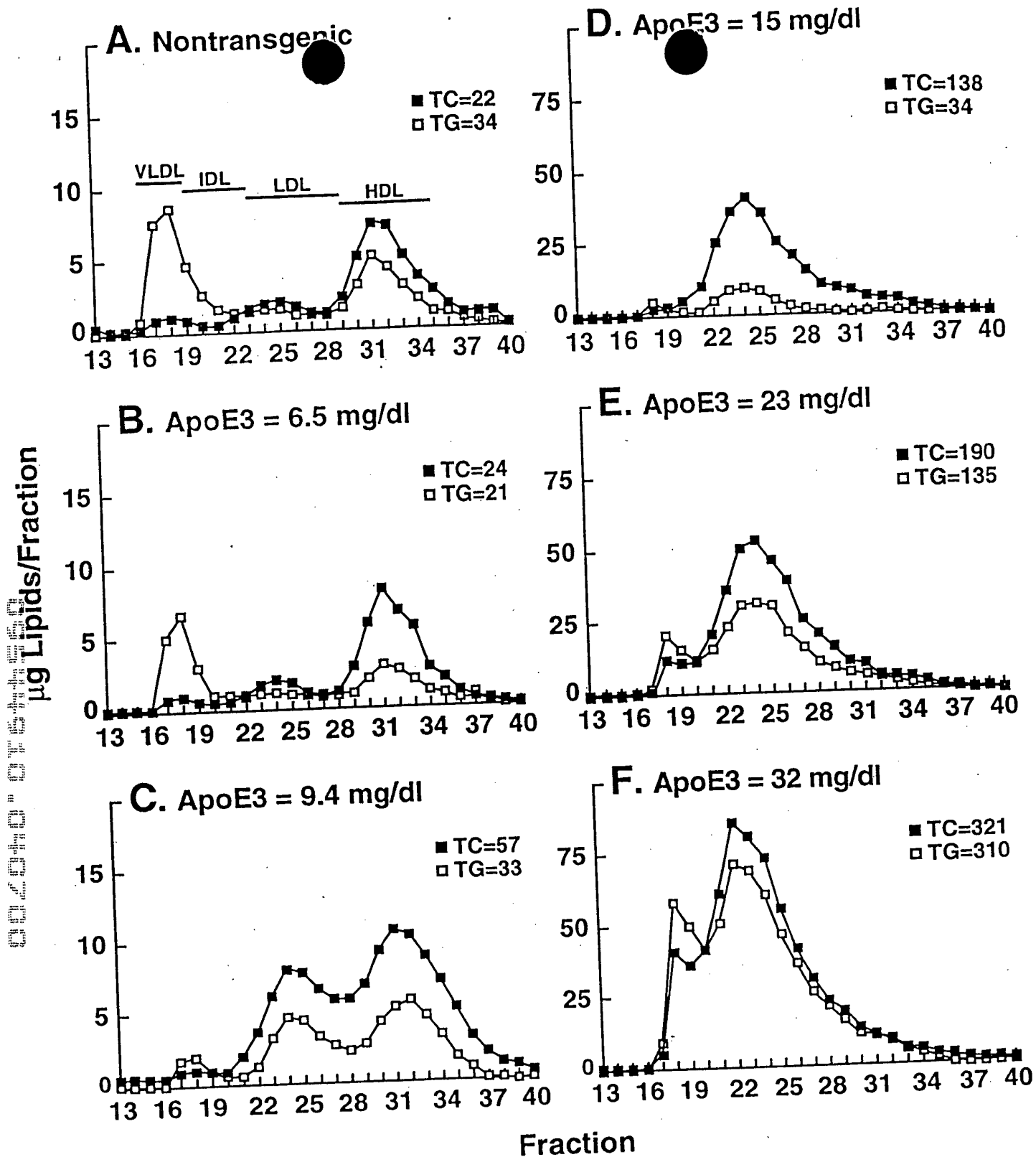


FIG. 9

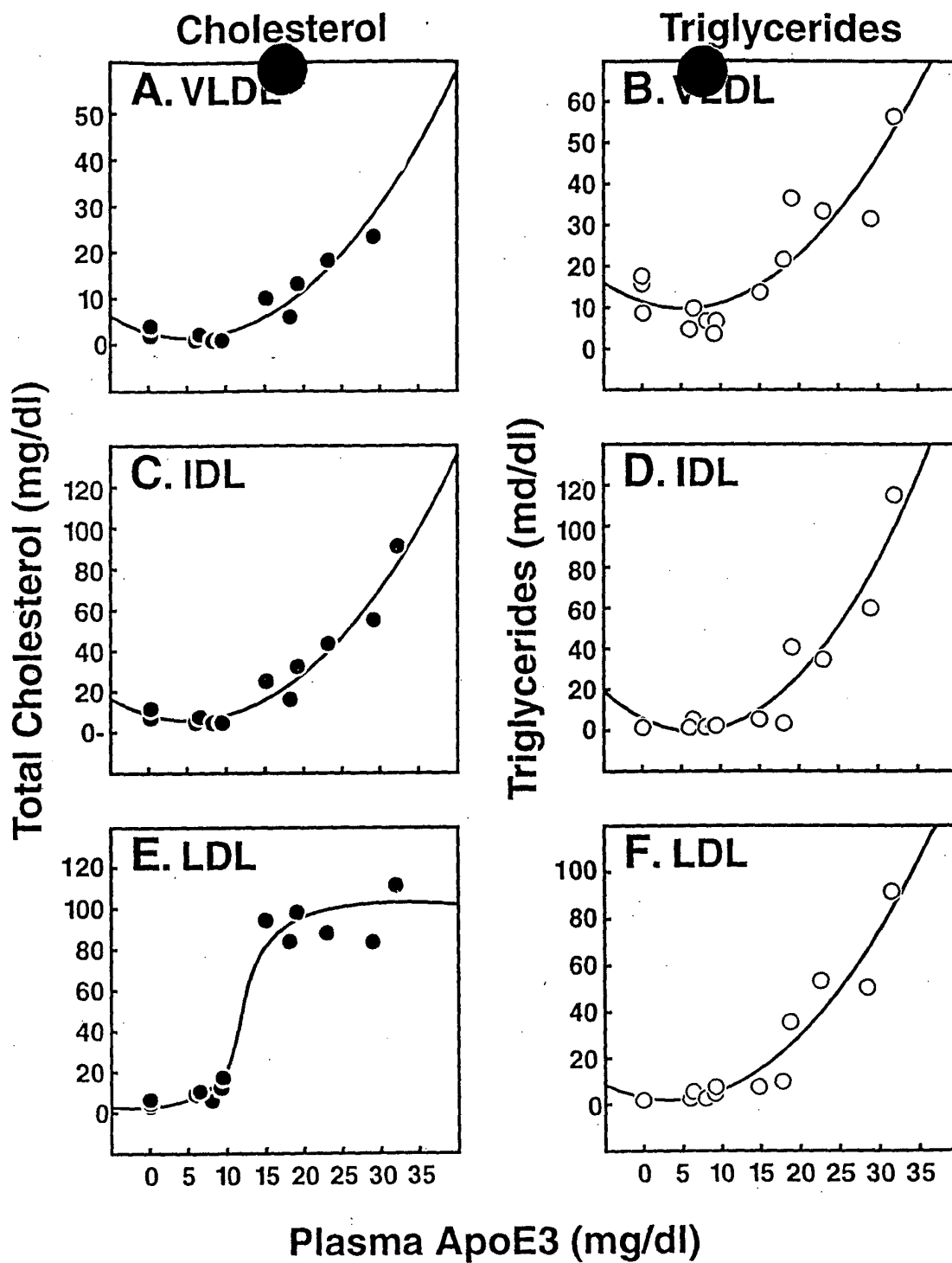


FIG. 10

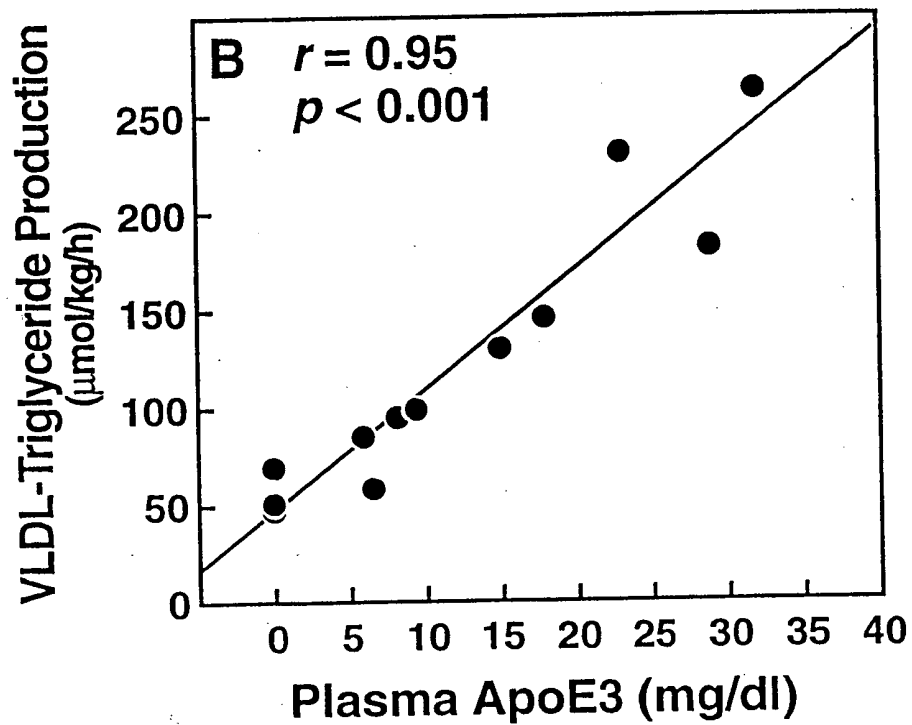
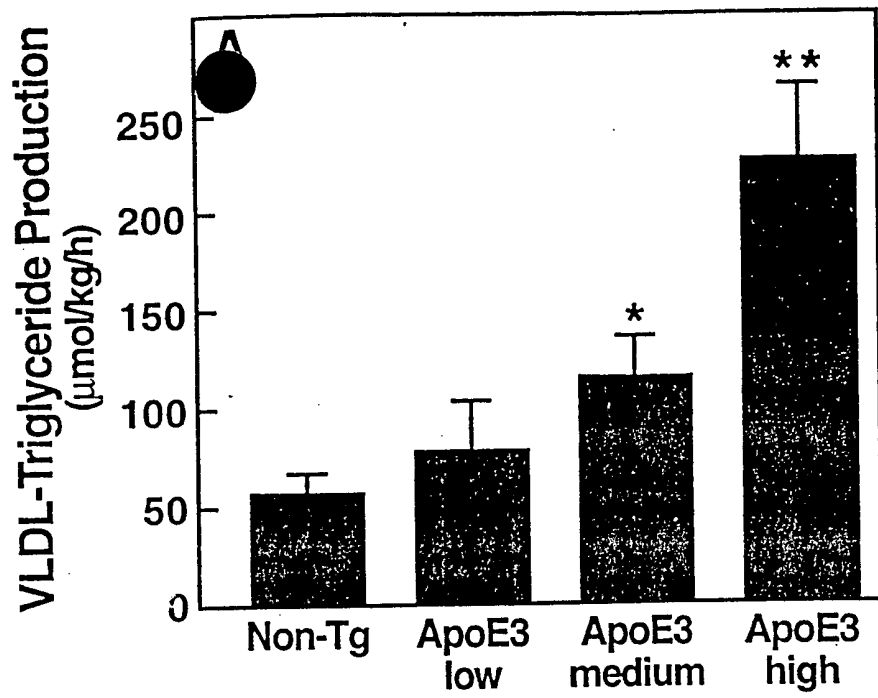


FIG. 11

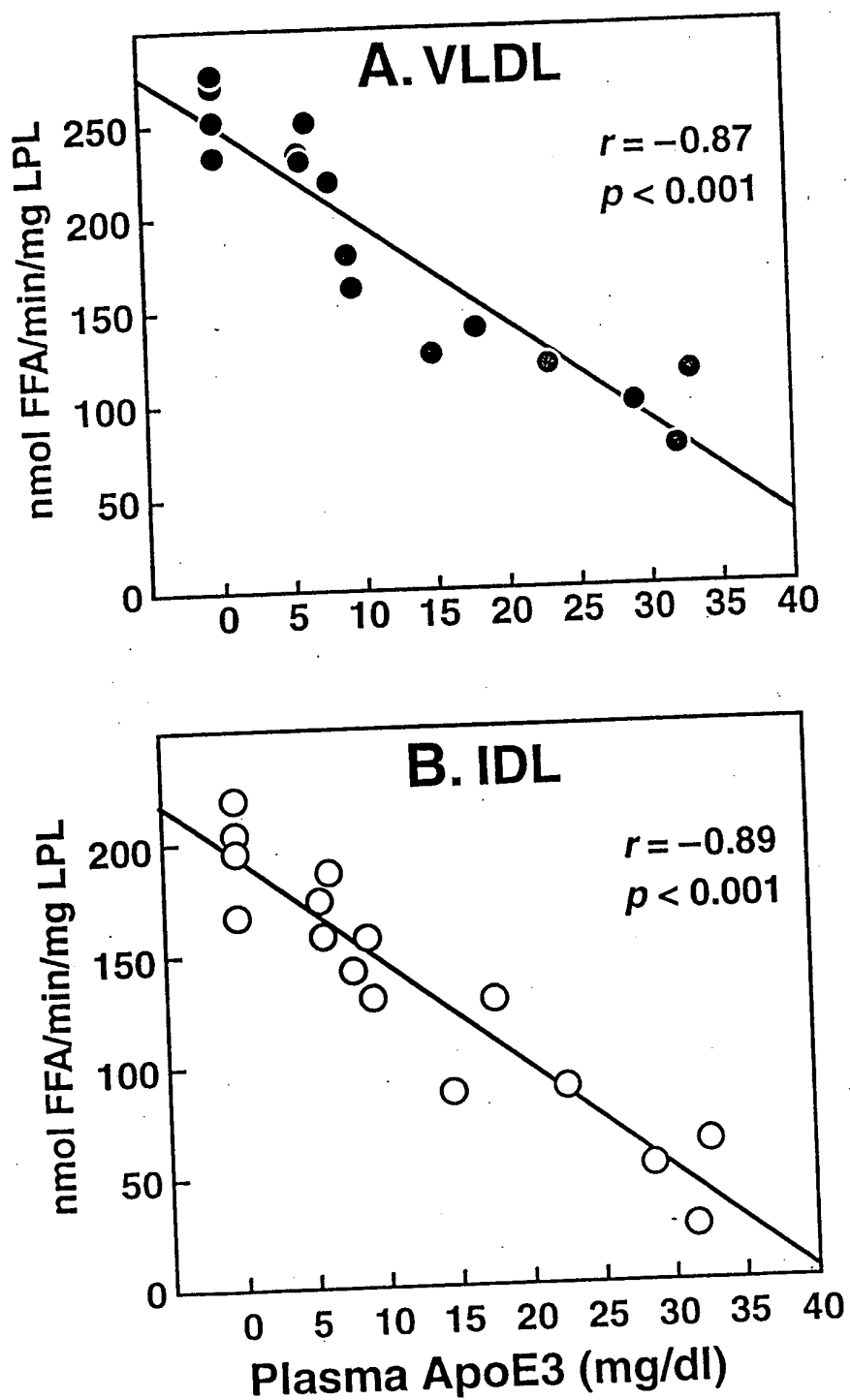


FIG. 12.

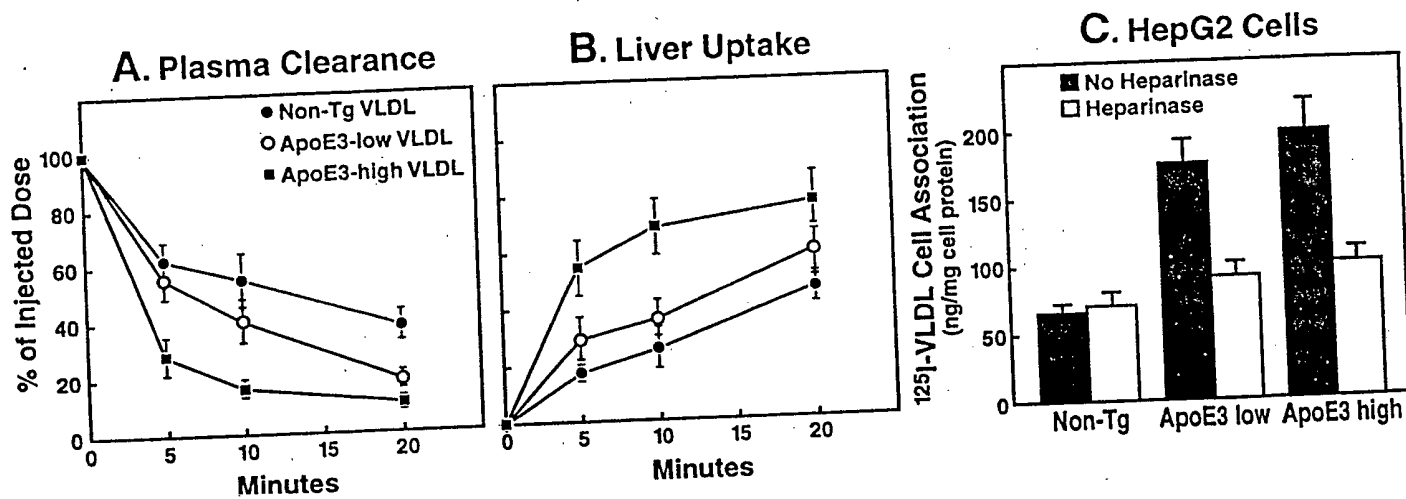
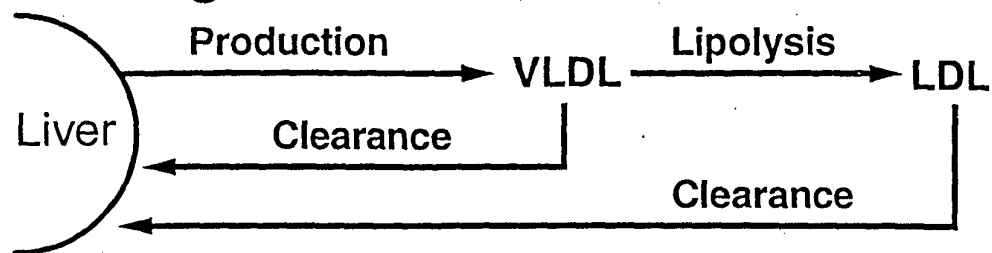
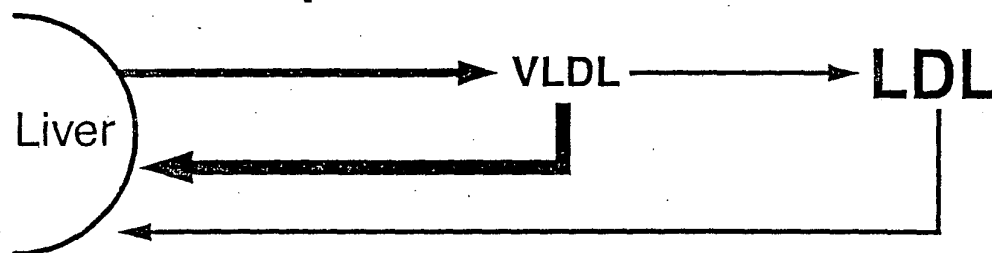


FIG. 13

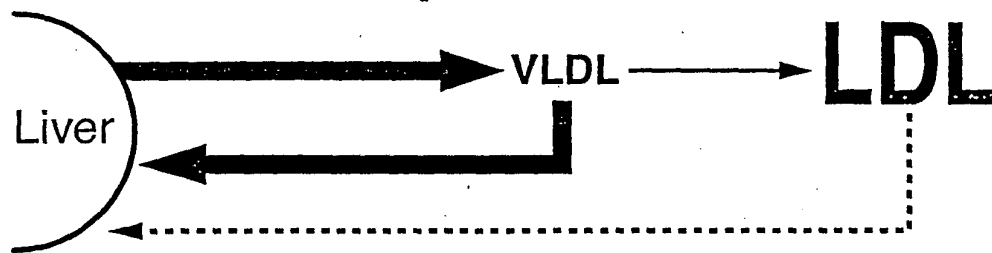
Nontransgenic



ApoE3 low expresser



ApoE3 medium expresser



ApoE3 high expresser

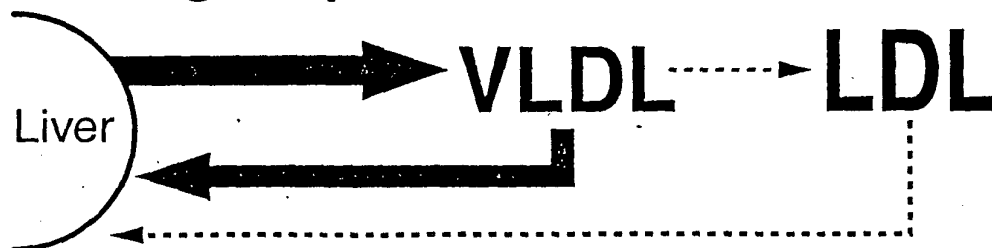


FIG. 14

TABLE IV

Plasma Lipid Levels of ApoE3 Transgenic Rabbits

Rabbits were analyzed at 8–12 months of age. TC, total cholesterol; TG, triglyceride.

| | <i>n</i> | ApoE3 | TC <i>mg/dl</i> | TG |
|-------------------------------|----------|--------|-----------------------|-----------------------|
| MALE | | | | |
| Nontransgenic | 4 | 0 | 26 ± 5 | 42 ± 27 |
| ApoE3 low (<10 mg/dl) | 6 | 8 ± 2 | 37 ± 18 | 26 ± 15 |
| ApoE3 medium (10–20 mg/dl) | 5 | 15 ± 4 | 109 ± 49 ^a | 72 ± 48 |
| ApoE3 high (>20 mg/dl) | 6 | 28 ± 4 | 224 ± 73 ^b | 198 ± 74 ^b |
| FEMALE | | | | |
| Nontransgenic | 4 | 0 | 38 ± 8 | 31 ± 6 |
| ApoE3 low (<10 mg/dl) | 4 | 8 ± 1 | 49 ± 6 | 25 ± 9 |
| ApoE3 medium (10–20 mg/dl) | 3 | 14 ± 4 | 108 ± 40 ^a | 83 ± 54 |
| ApoE3 high (>20 mg/dl) | 3 | 29 ± 2 | 182 ± 26 ^b | 154 ± 33 ^b |

^a*p* < 0.05 versus nontransgenics.

^b*p* < 0.005 versus nontransgenics.

FIG. 15